REMARKS

Claims 1-50 are pending in the instant application, with claims 3, 10-13, 17-22, 44, and 45 having been withdrawn from consideration. Claims 41, 43, and 46 have been amended, and claims 51 and 52 have been added. Accordingly, claims 1-52 will be pending in the application upon entry of the instant Amendment presented.

Support for the amendment to claims 41, 43 and 46 can be found throughout the specification and clams as originally filed and at least, for example, in claims 41-43 and 46 as originally filed. New claim 51 is directed to the recombinant cells corresponding to the elected species. Support for the addition of claim 51 can be found at least, for example, in the claims as originally filed and in the specification on page 3 (full page). Support for the addition of claim 52 can be found at least for example in claims 8, 10-13 and 44 as originally filed. No new matter has been added.

Cancellation of and/or amendments to the claims as originally filed should in no way be construed as an acquiescence to any of the rejections/objections set forth in the instant Office Action, and were made solely to expedite prosecution of the above-identified application. Applicants reserve the right to pursue the claims as originally filed, or similar claims, in one or more patent applications.

Attached hereto as Appendix A is a marked-up version of the changes made to the claims by the current amendments. Appendix A is captioned "Version with markings to show changes made." For the convenience of the Examiner, the claims that will be pending upon entry of the instant Amendment are attached hereto as Appendix B.

Restriction Requirement

The Office Action indicates that Applicants' arguments in traversing the restriction requirement have been considered but are not deemed persuasive. However, Applicants reiterate that, at least in the context of a recombinant ***yeast*** cell, the subject matter of the claims represent different embodiments of a single inventive concept for which a single patent should issue. At a

minimum, the pending claims directed to recombinant yeast cells represent an intricate web of knowledge, continuity of effort, and consequences of a single invention, which merit examination of all embodiments of the invention in a single application. For example, claims 10-13 are linked by a single, searchable, unifying aspect; *i.e.*, genes that encode proteins that activate the yeast pheromone response pathway.

Applicants submit that a search of such genes in the context of recombinant yeast cells would not be overly burdensome. In contrast, requiring Applicants to file and prosecute five additional applications to obtain claims directed to STE4, STE11, STE12, STE20 and FUS3 would be unreasonably burdensome and expensive to Applicants. Therefore, Applicants respectfully request that these aspects of the invention be rejoined. In the hope that the Examiner will be agreeable to such rejoinder, and also based on the proposed allowable claim helpfully suggested by the Examiner, claim 52 has been added. Applicants submit that claim 52 is allowable.

Claim Rejections – 35 U.S.C. § 112

Rejection of Claims under 35 U.S.C. § 112, First Paragraph

Claims 1, 2, 4-9, 14-16, 23-40, and 46-50 are rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. In particular, the Office Action, at pages 3-4, sets forth the allegation that:

> "the specification, while being enabling for a yeast cell comprising an STE2 G-protein coupled receptor, a FUSI-LacZ reporter construct, a FUSI-STE5 construct wherein the STE5 does not contain a hypersensitive mutation, does not reasonably provide enablement for a cell comprising a heterologous DNA construct comprising a gene encoding a protein that activates a signal transduction pathway, which gene is operably linked to a promoter that is responsive to activation of the signal transduction pathway, wherein said gene in not STE5. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims..... The claims encompass a

> practically limitless number of potential assays systems wherein different components of the yeast pheromone response signal transduction cascade are mixed and matched such that a positive feedback loop is established by at least one of the members of the cascade. However, the specification provides merely an invitation to the skilled artisan to try and find those components which might ultimately work together and also to try to find the correct expression systems, *e.g.* high or low copy plasmids, to get those components to work together."

Applicants respectfully traverse this rejection. Applicants submit that lever of skill in the art is very high and that area of technology is relatively predictable. Therefore, Applicants respectfully assert that the disclosure of the instant application, when combined with what was known to one of ordinary skill in the art at the time the application was filed, fully enables one of skill in the art to make and use the claimed invention without undue experimentation.

The Examiner's attention is invited to page 16, lines 16-41, of the specification where the general process for amplification of signaling *via* the pheromone response pathway is described. The specification further describes amplification of the yeast pheromone response pathing using Ste5 in Example 1 on page 66 of the specification. Example 1 is a working example, wherein the FUS1 promoter drives the expression of Ste5 in response to activation of a heterologously expressed C5a receptor.

Depending on the specific heterologous G-protein couple receptor, the instant specification describes combination of conditions that would be optimal to practice the claimed invention (see pages 13-22 of the specification). However, contrary to the assertion in the Office Action, there is a reasonable expectation of success using any of the combinations of conditions described in the present invention. For example, it is standard practice to use both high and low copy number plasmids, in an attempt to define optimal conditions.

With apparent reference to the "Wands factors", the Office Action, on page 4, indicates that:

> "[o]ne of skill in the art of intracellular signal transduction appreciates that this field is extremely complex, and, as the transduction components are often in a delicate balance with each

> other, these systems are also extremely unpredictable. It is simply beyond the skill of one highly skilled in the art to predict what the effect of the introduction of a positive feedback loop into one of these systems will have, *e.g.* rate limiting factors can be titrated out of the cascade or constitutive saturation of the response can occur due to high basal expression of any members of the cascade."

Applicants submit that the level of skill in the art in the area of recombinant cells having amplified signal transduction pathway responses is quite high, and the area of technology is relatively predictable. Applicants further submit that, for a particular system, the exemplified mutations or modifications as described in the claimed invention would be most useful, and would lead one of ordinary skill in the art to a number of other mutated proteins and modifications that would be useful in practicing the invention.

For example, Applicants teach which proteins activate the yeast pheromone response pathway and, accordingly, those proteins that can be used in the recombinant cells of the present invention (see page 3, line 32 through page 4, line 6 of the specification). Applicants further describe potential assay systems, for example, by teaching which pheromone-responsive promoter may be used to drive expression of the protein that activates the pheromone response pathway (see page 4, lines 10-15 of the specification). Furthermore, Applicants teach, for instance, that the endogenous gene that is mutated encodes a phosphatase that negatively regulates the yeast pheromone system pathway and provide examples of such phosphatases (see page 4, lines 12-15 of the specification).

More particularly, the Examiner's attention is also invited to the following sections of the specification:

- Page 17, line 32 through page 18, line 5, where Applicants describe a number of proteins that activate the pheromone system pathway, and that can be overexpressed in the yeast cells using a genetically engineered DNA construct, and the genes that code for those proteins.

- Page 18, lines 8-12, where Applicants describe a number of pheromone responsive promoters which can be used to drive the expression of components which activate the yeast pheromone system pathway.

• Page 18, lines 12-27, where Applicants describe a number of strategies by which ligand-generated signals may be amplified by genetically engineering positive feedback loops at various levels of the pheromone response pathway.

• Page 18, lines 28-42, where Applicants teach that the genetic construct carrying the gene encoding the activator protein, operatively linked to the pheromone responsive promoter, is carried by a plasmid, and that it may be desirable to control the copy number of the genetic construct. Applicants also provide strategies for controlling the copy number of the genetic construct.

• Page 19, lines 5-42, where Applicants teach that a mutant form of a protein that activates the pheromone response pathway is used, and which mutant form is expressed in the yeast host cell to allow for amplification of signaling by the pheromone pathway. Applicants also describe the phenotype expressed by these mutants (for example, proteins that exhibit constitutive activity and/or proteins that have activity in the absence of activation by upstream components of the pheromone signaling pathway), and how such mutants are made.

• Page 20, lines 20-40, where Applicants teach that in addition to overexpressing in the yeast cells a protein that activates the yeast pheromone system pathway, the yeast cells can be modified such that an endogenous yeast gene encoding a protein that negatively regulates the yeast pheromone system pathway is mutated to render the protein nonfunctional. Applicants go on to describe how yeast cells can be so modified, for example by inhibiting proteins that negatively regulate signaling via the pheromone response pathway.

• Page 21, line 37 through page 22, line 6, where Applicants teach that standard molecular biology techniques can be used to create genetic constructs carrying a gene that activates the pheromone response pathway, operatively linked to a pheromone responsive promoter, including the mutant forms of the gene. Working Examples 1 and 2 in the application are exemplary descriptions of the preparation of such constructs. Applicants also teach that standard cell transfection techniques can be used to introduce such constructs into the yeast host cells, and further that standard methods for deleting or specifically mutating endogenous yeast genes can be used to generate deletion or point mutants.

Applicants submit that these teachings do in fact enable one of ordinary skill in the art to make and use the invention as claimed without undue experimentation. Although these teachings are directed in large part to recombinant yeast cells and the pheromone response pathway, Applicants assert that these teachings constitute a blue print that enables the skilled artisan to practice the invention across a wide range or cell types and signal transduction pathways without undue experimentation.

The Office Action, at pages 5-6, also makes reference to a paper by Francis J. *et al.* (Society for Neuroscience Abstracts 26(1-2) abs. no. 49.16, 2000) to controvert that truth of the extension of Examples 1 and 2 of the instant application to other proteins. However, Applicants submit that there is nothing in this paper that conclusively establishes that Applicants' invention would not work in the system described in the Francis *et al.* paper. Moreover, Applicants respectfully submit that the disclosure of invention as set forth in their application must be given the presumption of correctness and operativeness by the PTO, and the only relevant concern of the PTO under the circumstances should concern the truth of the assertions contained in the application. *In re Marzocchi*, 439 F.2d 220, 169 U.S.P.Q. 367 (C.C.P.A. 1967); see also, *In re Bowen*, 492 F.2d 859, 181 U.S.P.Q. 48 (C.C.P.A. 1974). However, the Office Action proffers nothing but a mere conclusion drawn from a single literature paper to controvert the truth of Applicants' assertions in the instant application.

Furthermore, Applicants again point out that the instant application provides at least two working examples with regard to amplification of the yeast pheromone response pathway. (See Examples 1 and 2). Nevertheless, the Office Action in effect would impose an additional requirement for enablement, a requirement not found in the statute; *i.e.*, a working example for every claimed embodiment. However, Applicants assert that a working example is not a requirement for enablement (See, *Shanks v. Scheffer*, 204 U.S.P.Q. 781, 783 (Pat. Bd. Inter. 1979). Moreover, "there is no magical relation between the number of representative examples and the breadth of the claims." *In re Borkowski and VanVenroy*, 164 U.S.P.Q. 642, 646 (C.C.P.A. 1970). Section 112 only requires that the "specification contain a written description of the invention, and the manner and process of making and using it."

The key question then, is whether it would require undue experimentation to make and use the claimed compounds. Enablement is not precluded by the necessity for some experimentation, and a considerable amount of experimentation is permitted. See, *In re Wands*, 8 U.S.P.Q. 2d 1400, 1404 (Fed. Cir. 1988). Based on the teachings of the specification as enumerated and cited above and the state of the art at the time the application was filed, Applicants submit that one skilled in the art would be able to make and use the claimed compounds without undue experimentation.

Claim Rejections – 35 U.S.C. § 102

Rejections of Claim 41 under 35 U.S.C. § 102(a) and (e)

Claim 41 is rejected under 35 U.S.C § 102(a) and (e) as being anticipated by U.S. Patent No. 5691188 ('188). Applicants respectfully traverse the foregoing rejection. Applicants submit that the rejection no longer applies to claim 41 as amended herein. Therefore, Applicants respectfully request reconsideration and withdrawal of the rejection.

Claim Rejections – 35 U.S.C. § 103

Rejections of Claims 42 and 43 under 35 U.S.C. § 103(a)

Claims 42 and 43 are rejected under 35 U.S.C 103(a) as being unpatentable over the '188 patent in view of Doi, K., *et al.* Applicants respectfully traverse the rejection and submit that the Office Action fails to set forth a *prima facie* showing of obviousness.

To establish a *prima facie* case of obviousness for the claimed invention, there must first be some suggestion or motivation, either in the cited references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings in the manner proposed by the Examiner. Second, there must have been a reasonable expectation of success at the time the invention was made. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. See M.P.E.P. 2143. The prior art must suggest "to those of ordinary skill in the art that they ***should*** make the claimed composition or device, or carry out the claimed process" and "[b]oth the

suggestion and the reasonable expectation of success ***must be founded in the prior art, not in the applicant's disclosure*** (emphasis added)." *In re Dow Chemical Co.* 837 F.2d 469. 473, 5 U.S.P.Q.2d 1529, 1531 (Fed.Cir. 1988).

The Office Action cites patent '188 for the proposition that "mutations in genes known to be involved in adaptation (desensitization) of the pheromone response are useful for further amplifying the signal." The invention of the '188 patent is distinguishable from the claimed invention, because the '188 patent does not teach an endogenous yeast gene which encodes a phosphatase. The Examiner's attention is invited to page 16, line 29 through page 17 line 6 of the specification, wherein the Applicants describe that negative regulators of the pheromone response pathway, *e.g.* phosphatases, may be inhibited by mutation or deletion.

The Office Action also cites Doi, *et al.* for the proposition that "loss of msg5 function leads to diminished adaptive response to pheromone." The Office Action further cites patent '188 for teaching that "mutations in genes known to be involved in adaptation (desensitization) of the pheromone response are useful for further amplifying the signal."

Thus, the Office Action sets forth the following conclusion:

> "it would have been obvious to one of ordinary skill in the art at the time the invention was made, with reasonable expectation of success to use yeast cells having a mutation in the msg5 gene as taught by Doi, K., *et al.* when practicing the invention of U.S. Patent No: 5691188. The motivation to do so was taught by U.S. Patent No: 5691188 wherein it was stated that mutations in genes involved in pheromone response desensitization are useful for practicing the invention, see lines 23-36 of col. 2."

Applicants respectfully traverse the rejection.

Applicants respectfully submit that the Office Action mischaracterizes the teachings of the '188 patent. The '188 patent teaches that mutations in genes known to be involved in the mating signal transduction pathway, which is specifically defined in the patent as a kinase cascade (see col.1, l. 67 through col. 2, l.5), are useful for further amplifying the signal. Thus, the mutations envisioned by the '188 patent are limited to those genes which are known to be involved in the transduction pathway, *i.e.*, the protein kinase cascade.

The Office Action does not sufficiently establish a motivation to combine the '188 patent and the Doi, *et al.* reference. To properly combine references, an objective teaching leading to the combination must be shown. *In re Dembiczak*, 175 F.3d 994 (Fed. Cir. 1999). "The showing must be clear and particular....Broad conclusory statements regarding the teaching of multiple references, standing alone, are not 'evidence.'" *Id.*

According to the '188 patent, the mating signal transduction pathway is a protein kinase casade (column 1, line 67 through column 2, lines 5 of the '188 patent). Furthermore, introduction of mutations in this pathway, *i.e.*, a protein kinase casade, results in a yeast cell well suited for expression of a heterologous G-protein coupled receptor and able to functionally respond to cognate ligands (column 2, lines 30-36 of the '188 patent). There is no teaching or suggestion in the '188 patent to mutate a gene that codes for a protein kinase and/or that codes for a protein that is not a direct element of the signal cascade.

In contrast, msg5 is not a protein kinase, but is a protein tyrosine phosphatase, and therefore not a ***direct*** element of the protein kinase casade contemplated by the '188 patent. In fact, in the abstract, Doi *et al.* state:

> "Genetic analysis indicates that MSG5 acts at a stage where the protein kinases STE7 and FUS 3 function to transmit the pheromone-induced signal. Since loss of MSG5 function causes an increase in FUS3 enzyme activity but not STE7 activity, we propose that MSG5 ***impinges*** on the pathway at FUS3." [Emphasis added.]

Thus, one skilled in the art would not be motivated to use a mutated form of msg5 to practice the invention of patent '188. Based on the foregoing arguments, Applicants assert that the Office Action fails to make out a *prima facie* case of obviousness. Because Applicants have cancelled claim 42 without prejudice, Applicants respectfully request reconsideration and withdrawal of the rejection of claim 43 under 35.U.S.C. § 103(a).

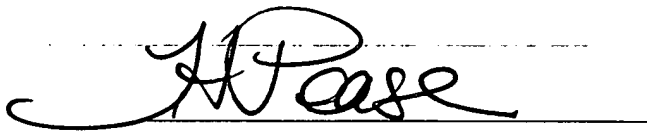
Allowable Subject Matter

Applicants note with appreciate the indication of allowable subject matter and the Examiner's helpful suggestion of a claim that would be considered allowable. In accordance with the Examiner's helpful suggestion, claim 51 has been added.

CONCLUSION

In view of the foregoing, Applicants respectfully request entry of the amendments and arguments presented herein, favorable reconsideration and withdrawal of all the rejections, and allowance of the application with the claims presented herein. If a telephone conversation with Applicants' attorney would help expedite the prosecution of the above-identified application, the Examiner is urged to call Applicants' attorney at (617) 227-7400.

Respectfully submitted,



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